AMENDMENTS

In the claims:

Please amend claim 2, such that the text of the amended claim reads as follows:

1. (previously presented) An isolated nucleic acid molecule comprising the nucleotide sequence of the ion exchanger of SEQ ID NO: 1.

2 (presently amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

a. encodes the amino acid sequence shown in SEQ ID NO: 2; and
b. hybridizes ~~under highly stringent conditions~~ to the nucleotide sequence of SEQ ID NO:1 or the complement thereof.

3.(original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4.(original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:4.

5. (previously presented) A recombinant expression vector comprising the nucleic acid molecule of claim 3.

6. (previously presented) A recombinant expression vector comprising the nucleic acid molecule of claim 4.

7. (previously presented) A host cell comprising the recombinant expression vector of claim 5.

8. (previously presented) A host cell comprising the recombinant expression vector of claim 6.

9. (new) The isolated nucleic acid molecule of claim 4 wherein said nucleic acid sequence is that of SEQ ID NO:3.

RESPONSE

I. Status of the Claims

Claim 2 has been amended as requested by the Examiner and to further clarify the claim. Dependent claim 9 has been added to better claim the present invention. Claims 1-9 are therefore pending in the present case.

II. Support for the Amended Claims

Claim 2 has been amended as requested by the Examiner and to further clarify the claim. Amendment of claim 2 finds support throughout the specification as originally filed with particular support for hybridization being found on or about the specification at page 4, line 32.

Dependent claim 9 has been added to better claim the present invention. Claim 9 finds support throughout the specification and sequence listing as originally filed with particular support from original claim 4 and SEQ ID NO:3.

As the amendment of claim 2 and new claim 9 are fully supported by the specification, sequence listing and claims as originally filed, they do not constitute new matter. Entry is therefore respectfully requested.

III. Rejection of Claims Under 35 U.S.C. § 101

The Action rejects the claims under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants strongly disagree, and continue their traverse by summarizing some previously presented arguments and elaborating on others, while attempting to maintain the Examiners alphabetical identification of the issues used within the Final Action. In some cases as topics are similar these letters appear out of order.

Issue **(a)** requires no comment.

Issue **(b)** challenges the tissue expression data presented with in the specification, first paragraph of Section 5, on or about line 8 on page 4. The Final Action (page 4 first paragraph) states that it is unclear from which species the samples were taken and further suggests that no actual

expression evidence is provided in the specification as the information is prophetic rather than actual as it clearly states, "which may be expressed (pp.4 line 9). Thus no evidence is presented...".

First, Applicants point out that the title of the Application clearly refers to human ion-exchanger proteins and thus it follows that the most likely and most meaningful expression evidence would, of course, be human expression information. Furthermore, the expression listing begins with the phrase human cell lines. Therefore, it should not be surprising to find that the expression evidence described in the present application was the result of RT-PCR based identification of specific transcripts present in cDNA that was obtained from 50 different normal and cancerous human cell lines derived from human tissue. Of the 50 human tissues examined only the 17 tissues described in the specification were convincingly positive for expression of the sequences of the present invention by RT-PCR.

Applicants acknowledge that the phrase " may be expressed" was used, however in the present situation it does not mean that the evidence presented was prophetic, rather, the phrase was used to maintain scientific accuracy. As would be clearly understood by those of skill in the art, that while Applicants did find the sequences of the present invention to be present in the tissues described and not in others tested, they can not say with 100% certainty that this will be true of cell lines derived from the similar tissues or for that matter from fresh human tissue samples or tissues derived from different individual humans will yield identical expression results. It is well known to those of skill in the art that all scientific techniques have technical limitations and that the limitations of RT-PCR are well. Therefore, as Applicants can not categorically state that the sequences of the present invention will always be present in the tissues in which they were identified, in order to accurately portray the evidence in this specification, given these well recognized limitations, the phrase "may be expressed in" was used and those of skill in the art would readily understand and accept this.

Issue **(c),** while acknowledging Applicants' previous rebuttal of the "evidence" provided, reiterates that Applicants' assertion can not be substantial if it is based on sequence alignment and homology. This position runs contrary to Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55) which accepts high degrees of homology. The Final Action (page 4, lines 9-10) also notes that "no evidence was presented to support a credible, specific, and substantial utility for SEQ ID NO:1, 2, or 4."

While the Examiner has apparently recognized Applicants' continued assertion that the sequences of the present invention encode a sodium-calcium (Na+/Ca+)exchanger protein, for the

record Applicants reiterate some of the evidence provided in the specification as filed supporting their assertion. Several of the clearest examples in the specification supporting Applicants' assertion that the sequences of the present invention encode a human sodium-calcium exchanger protein are: in the title of the application "NOVEL HUMAN ION-EXCHANGER PROTEINS AND POLYNUCLEOTIDES ENCODING THE SAME"; on page 1, lines 10-12 is the statement identification, and characterization of novel human polynucleotides encoding a novel human ion exchanger protein"; in Section 2 (page 1, line 25 through page 2, line 10) the well-recognized function of ion exchanger proteins are described; and on page 2, lines 17-19 of the specification, it is stated that the proteins encoded by the sequences of the present invention share structural similarities with known mammalian exchanger proteins such as sodium-calcium exchanger proteins and potassium dependent versions of the same. Thus, clearly Applicants have asserted that the sequences of the present invention encode a novel human sodium-calcium exchanger protein.

As evidence supporting the credibility of Applicants' assertion that the sequences of the present invention encode a sodium-calcium (Na+/Ca+) exchanger protein, and variants thereof, is the amino acid sequence comparison (presented in Applicants' previous Response as Exhibit B) between SEQ ID NO:2 and an amino acid sequence that is identical to SEQ ID NO:2 of the present invention that is present in the leading scientific repository for biological sequence data (GENBANK). This sequence, GENBANK Accession No. AF510501 (presented in Applicants' previous Response as Exhibit C) has been annotated by third party scientists *wholly unaffiliated with Applicants* as "Homo sapiens Na+/Ca+ exchanger isoform 3 splice varient 2 (SLC8A3). This sodium-calcium exchanger protein is described in publications by Gabellini, *et al.* (Gene, **298**:1-7, 2002 presented in previous Response as Exhibit D) and Gabellini, *et al.* (J Neurochem, **84**:282-293, 2003 and Ann NY Acad Sci, **976**:282-4, 2002, **Exhibit B**). These publications constitute additional evidence that clearly demonstrates that the ion exchanger proteins of the present invention have function and utility that are both accepted by those skilled in the art. As the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. In the present instance, the Examiner has argued that in spite of shared structural features that those skilled in the art would not believe that a protein has a given biochemical activity. Clearly those of skill in the art would recognize that molecules that share identical amino acid sequences would share identical protein structure and would thus also have identical functions. Given this clear evidence that those

skilled in the art have independently assigned Na+/Ca+ exchanger function and activity there can be no question that Applicants' asserted utility for the described sequences is "credible" and constitutes a post filing date evidence that clearly supports Applicants' assertion in the specification that the sequences of the present invention encoded sodium-calcium (Na+/Ca+) exchanger proteins.

Issue **(g),** while acknowledging that "These Exhibits show that the assertion that SEQ ID NO: 1, 2 and 4 are Na+/Ca exchanger is credible. This is accepted by the Examiner." However, this is not deemed sufficient to establish specific and substantial utility.

Applicants note that MPEP 2107 (II)(B)(1) states:

> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

Given Applicants assertions and that SEQ ID NO:2 is identical to a recognized sodium-calcium exchanger, Applicants respectfully submit that the present situation directly parallels Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity to a protein having a known function. The function of sodium-calcium (Na+/Ca+) exchanger proteins are well known and were even described in the specification as filed.

In the Analysis portion of Example 10 it states that "Based on applicant's disclosure and the results of the PTO search, **there is no reason to doubt** the assertion that SEQ ID NO:2 encodes a DNA ligase. Further DNA ligases have a well-established use in the molecular biology art based on this class of proteins ability to ligate DNA. .....Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed..... Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made."

The present case is identical to that presented in Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55). In the present case it is clear from the amino acid comparison (previously presented in Applicants Response as Exhibit B in Paper No. 9) that the protein encoded by SEQ ID NO:2 is identical to the protein described in GENBANK Accession No. AF510501, a sequence annotated by others in no way affiliated with Applicants to be an ion-exchanger protein, more specifically ion-exchanger Homo sapiens Na+/Ca+ exchanger isoform 3 splice varient 2 (SLC8A3). Thus, clearly those of skill in the art would accept that identical protein structures have identical activity and thus the sequences of the present invention encode a human sodium-calcium (Na+/Ca+) exchanger protein (SLC8A3).

As sodium-calcium exchanger proteins have a well-established utility. According to the guidelines "Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed...Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made." Thus the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should not have been made and should thus be withdrawn.

Issue **(d)** deals with the repeated use by the USPTO Examiners of a handful of contrarian publications, many by the same individual, to discredit the value of structure-function analysis and bioinformatics. As Applicants detailed in their previous response, even these publications in fact see great value in bioinformatics. Applicants believe that, contrary to these few publications, bioinformatic information is valued by the vast majority of those of skill in the art, the scientific community and that the numerous and frequent publication of such information speaks to its value. Issue **(e)** deals with Applicants' above stated "belief" that the majority of those of skill in the art and the scientific community value bioinformatics and appears to be requesting evidence that those of skill in the art accept the structure-function relationship and bioinformatics.

Rather then overwhelm the USPTO's scanning division with even the abstracts of the 5,548 different scientific publications that result of a search of the NCBI-NLM-NIH public scientific database "PubMed" using the term "bioinformatics", Applicants respectfully submit as exemplary evidence a listing of the first 60 references(as **Exhibit A**) which have been published in the last few months alone as a representative sample of the many scientific publications that value bioinformatic information. Further Applicants note that there is a Journal entitled "Bioinformatics" (see no. 6 in the listing

provided) and that clearly this demonstrates the value those of skill in the art place on bioinformatic information.

Additional evidence supporting Applicants' "beliefs" regarding the value of bioinformatics include the fact that many scientists, corporations and institutions elect to allocate significant proportions of their limited resources for access to private bioinformatic systems and databases. Thus, it would appear obvious that if those of skill in the art value the results of bioinformatic analysis and are willing to pay dearly for access to such information that such information must have well recognized utility.

Furthermore, clearly indicative that those of skill in the art accept the value of bioinformatic information, is the fact that multiple US patents have been issued by the USPTO regarding bioinformatic prediction and methods for doing the same (see for example, U.S. Patent Nos. 6,229,911, 6,567,540, 6,615,141, 6,631,331, 6,651,008, 6,677,114, again these patents will not be provided to avoid burdening the USPTOs scanning group). Clearly, if as the Examiner alleges the provided examples indicate, that bioinformatic analysis is without merit, then such patents would not have issued. Clearly a method or system for doing something that those of skill in the art recognize is without merit would lack patentable utility and said patents would not have issued if such were the case. However, multiple such patents have issued and therefore bioinformatic analysis and findings as well as methods and systems for doing bioinformatic analysis have utility and must logically have merit.

Finally even the USPTO, at least in Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity score of 95% to a protein having a known function.

In summary, while it had been assumed that the value of bioinformatic information was readily recognizable, apparently the Examiner does not accept this. Therefore, multiple lines of evidence have been provided clearly demonstrating that those of skill in the art place significant value on bioinformatic analysis and the information it provides. Thus, clearly such an assertion was not simply based on Applicants "belief".

Issue **(f)** acknowledges Applicants submission of applicable case law regarding utility but is not persuaded by such.

Issue(**h**)refers to utilities described for the sequences of the present invention including the identified naturally occurring polymorphisms that occur within them. In addition to the well established utilities presented above, additional utilities for the sequences of the present invention include assessing temporal and tissue specific gene expression patterns (specification at page 7, line 19), particularly using a high throughput "chip" format (specification at page 6, line 25 through page 8). The Final Action, however, discounts Applicants' assertions regarding such uses of the presently claimed polynucleotides on DNA chips, perhaps based on the position that such a use would allegedly be generic. As set forth in Applicants' First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described sequences which encode variants of the human sodium-calcium exchanger protein (SLC8A3) which also contains identified polymorphisms (the second paragraph of Section 5.1 on page 17) and has been shown to be expressed in human cell lines, fetal brain, brain, pituitary, cerebellum, spinal cord, lymph node, lung, prostate, adrenal gland, skeletal muscle, esophagus, pericardium, hypothalamus, fetal kidney, tongue, 6-12 and 12 week embryos, and osteosarcoma cells. Thus, Applicants have identified nucleic and amino acid sequences which encode the human sodium-calcium exchanger protein (SLC8A3), which contains identified polymorphisms and a characterized tissue expression pattern.

DNA chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, like the present sequences, which encode a human sodium-calcium exchanger protein (SLC8A3), have identified polymorphisms and a characterized tissue expression pattern, must have utility. The sequences of the present invention which encode variants of the human sodium-calcium exchanger protein (SLC8A3), have identified polymorphisms and characterized tissue expression patterns provide specific markers for the human genome (see chromosome mapping evidence provided in the specification and with Applicants' prior response), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Accordingly, the present

sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

The Examiner is further requested to consider that, given the huge expense of the drug discovery process, even negative information obtained using these specific markers of expression of a human sodium-calcium exchanger protein (SLC8A3) with identified polymorphisms and a characterized tissue expression pattern provide very specific markers for the human genome and have great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of DNA gene chips, such as the presently claimed sequences encoding a human sodium-calcium exchanger protein (SLC8A3), must in themselves be useful. Moreover, the presently described human sodium-calcium exchanger protein (SLC8A3) provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

In the Final Action the position that the argument that the polymorphisms described in the specification have patentable utility is also deemed to be non-persuasive. This is allegedly because the asserted utilities of the present nucleic acid sequences and their identified polymorphisms in forensic analysis, human population biology, or paternity identification are not specific or substantial.

Naturally occurring genetic polymorphisms such as those described in the present specification are both the basis of, and critical to, *inter alia*, forensic genetic analysis and genetic analysis intended to resolve issues of identity and paternity. Therefore, Applicants find this position difficult to comprehend, given that the results of identity and paternal analysis often have great emotional and substantial economic impact. This does not sound like a throw away utility, rather it sounds like a very substantial and real world utility. What could be more substantial and real world than the loss of an individual's freedom through incarceration and in some cases even the loss of life through execution? Yet forensic analysis based on identified polymorphisms is often used to convict or acquit in many cases. Both paternal and forensic genetic analysis is based on the use of identified polymorphisms. This

is a well known and generally accepted by those of skill in the art, who would readily recognize the utility and value of any identified polymorphism. Without identified polymorphisms, one would not be able to carry out such forensic or paternal analyses. The present application has identified just such essential polymorphisms within the sequences of the present invention which identify variants of the human sodium-calcium exchanger protein (SLC8A3).

As such polymorphisms are the basis for forensic analysis, paternity identification and population biology studies, which are undoubtedly "real world" utilities, the present sequences must in themselves be useful. In and of themselves each of these polymorphisms, including the silent ones, has significant and specific utility, the specificity of this utility is only amplified by the presence of so many polymorphisms that can arise in various combinations. It is also important to note that the presence of more useful polymorphic markers for such analysis would not mean that the present sequences lack utility.

Applicants respectfully point out that those of skill in the art would readily recognize that the presently described polymorphisms, exactly as they were described in the specification as originally filed, are useful in forensic analysis, population biology and paternity analysis to specifically identify individual members of the human population based on the presence or absence of the described polymorphism. Simply because the use of these polymorphic markers will necessarily provide additional information on the percentage of particular subpopulations that contain one or more of these polymorphic markers does not mean that "additional research" is needed in order for these markers as they are presently described in the instant specification to be of use to forensic science. As stated above, using the polymorphic markers as described in the specification as originally field will definitely distinguish members of a population from one another. In the worst case scenario, each of these markers are useful to distinguish 50% of the population (in other words, the marker being present in half of the population). The ability to eliminate 50% of the population from a forensic analysis clearly is a real world, practical utility. Therefore, any allegation that the use of the presently described polymorphic markers is only potentially useful would be completely without merit, and would not support the alleged lack of utility.

Perhaps the Examiner assumes, correctly that as any human nucleic acid sequence that contains a naturally occurring polymorphism can be used in forensic analysis, in human paternity determinations

or human population migration determinations, such utilities are generic and lack substantial and specific utility in the absence of identification of the characteristics of populations bearing such polymorphisms. Applicants respectfully disagree, for without further experimentation those of skill in the art would recognize the utility of the identified polymorphisms and how the asserted markers can distinguish 50% of the population in the worst case scenario. Thus the presence or the absence of a particular specific polymorphism is sufficient for use in the proposed utilities. Applicants provide the following detailed explanation. Those of skill in the art would recognize that in the worst case, least useful situation, a marker would be present in half of a population and absent from the other half. Therefore the probability of an individual having such a marker would be 1 in 2 or 50%. Using the forensic analysis scenario for example, the analysis will have removed 50% of the possible suspects from the list, as either the suspect has the identified polymorphism or not. However, if a polymorphism were present in only say 10% of the population, the probability of an individual having such a polymorphic marker would be 1 in 10 (10%) and 90% of suspects could be eliminated from investigation or prosecution based on the presence or absence of the polymorphism. Clearly eliminating 90% of the suspects is better than eliminating 50% of the suspects. That said, eliminating 50% or half of the suspects on a list is without question very useful to any investigator.

Applicants submit that until a specific polymorphic marker is actually described it has very limited utility in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a specific polymorphism is actually identified and described, such a likelihood is meaningless. The present case contains identified polymorphisms that occur in a human sodium-calcium exchanger protein. The Examiner is perhaps attempting to use the information presented for the first time by Applicants in the instant specification as hindsight verification that the presently claimed sequence would be expected to have polymorphic markers. Such a hindsight analysis based on Applicants discovery would not be proper. Alternatively, the Examiner appears to be confusing the requirement for a specific utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a unique utility. The relevant case law cited by Applicants makes it abundantly clear that the presence of other or even more useful polymorphic markers for forensic analysis does **not** mean that the present sequences lack a specific utility. As clearly stated by the

Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Importantly, the holding in the *Carl Zeiss* case is mandatory legal authority that essentially controls the outcome of the present appeal. This case, and particularly the cited quote, directly rebuts any such argument. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Applicants respectfully submit that to be used in forensic or paternal genetic analysis a human nucleic acid must contain an identified polymorphism and in fact it is the multiple polymorphisms that occur within the sequences encoding this human ion-exchanger protein and described in the specification that would provide just such a group of "specific features", should they have been needed. The presently described polymorphisms are part of the family of polymorphisms that have a well

established utility and Applicants reliance on *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is not at all misplaced.

Additionally, as previously stated, only a small percentage of the genome (2-4%) actually encodes exons, which in turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. This further discounts the Examiner's position that such uses are "generic". The present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome (specification at page 12, line 3), for example mapping the protein encoding regions as described in the specification (page 3, line 19-20) and as evidenced in Applicants' previous response. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon

sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence supporting the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

Provided as evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in Applicants' previous response as Exhibit E. This is the result of overlaying the sequence of SEQ ID NO:1 of the present invention and the identified human genomic sequence. By doing this one is able to identify the portions of the genome that encode the present invention. If these regions of the genome are non-contiguous, this is indicative of individual exons. The results of such an analysis indicates that the sequence of the present invention is encoded by more than 6 exons spread non-contiguously along a region of human chromosome 14, (as stated in the specification as filed on page 18, lines 7-10) at approximately 14q24, which are contained within partially overlapping clones, AL160191.3 and AL135747.4. Thus clearly one would not simply be able to identify the 6 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were. Additionally, it should be noted that the human sodium-calcium (Na+/Ca+) exchanger, SLC8A3 gene also maps to the same region of human chromosome 14 (14q24). This further supports Applicant's position that the sequences of the present invention encodes a human sodium-calcium exchanger, SLC8A3. In addition, Applicants note that this region of human chromosome 14 has since been noted as containing the gene encoding the human sodium-calcium (Na+/Ca+) exchanger, SLC8A3, and as stated in the specification as filed.

Issue (i) refers to the issue of due process, an argument which Applicants maintain. However, as the Examiner has declined to comment on the issue, it will not be discussed further at this point.

In summary, the specification of the present invention describes, as was asserted in the application, sequences that encode a human sodium-calcium (Na+/Ca+) exchanger, specifically that known to the art as sodium-calcium exchanger protein (SLC8A3). Human sodium-calcium exchanger proteins in general and SCL8A3 have been recognized by those of skill in the art as having substantial, specific and credible utilities. Also described in the specification were naturally occurring polymorphisms that occur in these sequence and which are the basis of identifications used in resolving both forensic and paternity issues. Further, the sequences of the present invention, which encode SCL8A3, have particular utility in DNA chip analysis due to the tissue expression information and polymorphisms provided in the specification as filed. In addition, as described in the specification, these sequences were used to map that region of human chromosome 14 which encodes this human sodium-calcium exchanger protein (SLC8A3). Therefore, Applicants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of the pending claims under 35 U.S.C. § 101 should be withdrawn.

V. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action also rejects the pending claims under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as the sequences of the present invention have been shown to have a specific, substantial, credible and well established utility, as detailed in section IV above, Applicants therefore respectfully request that the rejection of claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Action further maintains the rejection of claim 2 under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. While Applicants do not agree, in order to more quickly advance the

application to allowance, claim 2 has been amended to remove the allegedly indefinite hybridization conditions. Thus this issue has therefore been rendered moot and the rejection has been avoided.

VII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Nichols have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

February 17, 2004
Date

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EXHIBIT A

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1: Karaulanov E, Knochel W, Niehrs C. Related Articles, Lir

Transcriptional regulation of BMP4 synexpression in transgenic Xenopus.
EMBO J. 2004 Feb 12 [Epub ahead of print]
PMID: 14963489 [PubMed - as supplied by publisher]

2: Rogers MA, Langbein L, Winter H, Beckmann I, Praetzel S, Schweizer J. Related Articles, Lir

Hair Keratin Associated Proteins: Characterization of a Second High Sulfur KAP Gene Domain on Human Chromosome 21.
J Invest Dermatol. 2004 Jan;122(1):147-58.
PMID: 14962103 [PubMed - in process]

3: Fleming JV, Sanchez-Jimenez F, Moya-Garcia AA, Langlois MR, Wang TC. Related Articles, Lir

Mapping of catalytically important residues in the rat L-histidine decarboxylase enzyme using bioinformatic and site directed mutagenesis approaches.
Biochem J. 2004 Jan 30 [Epub ahead of print]
PMID: 14961766 [PubMed - as supplied by publisher]

4: Svensson M, Lundh D, Ejdeback M, Mandal A. Related Articles, Lir

Functional prediction of a T-DNA tagged gene of Arabidopsis thaliana by in silico analysis.
J Mol Model (Online). 2004 Feb 7 [Epub ahead of print]
PMID: 14767695 [PubMed - as supplied by publisher]

5: Marmiesse M, Brodin P, Buchrieser C, Gutierrez C, Simoes N, Vincent V, Glaser P, Cole ST, Brosch R. Related Articles, Lir

Macro-array and bioinformatic analyses reveal mycobacterial 'core' genes, variation in the ESAT-6 gene family and new phylogenetic markers for the Mycobacterium tuberculosis complex.
Microbiology. 2004 Feb;150(Pt 2):483-496.
PMID: 14766927 [PubMed - as supplied by publisher]

6: King RD, Wise PH, Clare A. Related Articles, Lir

Confirmation of data mining based predictions of protein function.
Bioinformatics. 2004 Feb 5 [Epub ahead of print]
PMID: 14764546 [PubMed - as supplied by publisher]

7: del Val C, Mehrle A, Falkenhahn M, Seiler M, Glatting KH, Poustka A, Suhai S, Wiemann S. Related Articles, Lir

High-throughput protein analysis integrating bioinformatics and experiment

assays.
Nucleic Acids Res. 2004 Feb 03;32(2):742-8. Print 2004.
PMID: 14762202 [PubMed - in process]

☐ 8: Castrillo JI, Oliver SG. Related Articles, Lir

Yeast as a touchstone in post-genomic research: strategies for integrative analysis in functional genomics.
J Biochem Mol Biol. 2004 Jan 31;37(1):93-106.
PMID: 14761307 [PubMed - in process]

☐ 9: Yu U, Lee SH, Kim YJ, Kim S. Related Articles, Lir

Bioinformatics in the post-genome era.
J Biochem Mol Biol. 2004 Jan 31;37(1):75-82.
PMID: 14761305 [PubMed - in process]

☐ 10: Militello KT, Dodge M, Bethke L, Wirth DF. Related Articles, Lir

Identification of regulatory elements in the Plasmodium falciparum genom
Mol Biochem Parasitol. 2004 Mar;134(1):75-88.
PMID: 14747145 [PubMed - in process]

☐ 11: Brehm A, Tufteland KR, Aasland R, Becker PB. Related Articles, Lir

The many colours of chromodomains.
Bioessays. 2004 Feb;26(2):133-40.
PMID: 14745831 [PubMed - in process]

☐ 12: Weinstein JN, Pommier Y. Related Articles, Lir

Transcriptomic analysis of the NCI-60 cancer cell lines.
C R Biol. 2003 Oct-Nov;326(10-11):909-20.
PMID: 14744097 [PubMed - in process]

☐ 13: Soeria-Atmadja D, Zorzet A, Gustafsson MG, Hammerling U. Related Articles, Lir

Statistical Evaluation of Local Alignment Features Predicting Allergenicity Using Supervised Classification Algorithms.
Int Arch Allergy Immunol. 2004 [Epub ahead of print]
PMID: 14739578 [PubMed - as supplied by publisher]

☐ 14: Jiang XS, Zhou H, Zhang L, Sheng QH, Li SJ, Li L, Hao P, Li YX, Xia QC, Wu JR, Zeng R. Related Articles, Lir

A High-throughput approach for subcellular proteome: Identification of rat liver proteins using subcellular fractionation coupled with two-dimensional liquid chromatography tandem mass spectrometry and bioinformatic analysis.
Mol Cell Proteomics. 2004 Jan 22 [Epub ahead of print]
PMID: 14739257 [PubMed - as supplied by publisher]

☐ 15: Kawaji H, Takenaka Y, Matsuda H. Related Articles, Lir

Graph-based clustering for finding distant relationships in a large set of protein sequences.
Bioinformatics. 2004 Jan 22;20(2):243-252.
PMID: 14734316 [PubMed - as supplied by publisher]

☐ 16: Wang ZG, Li LJ, Luo Y, Zhang JY, Wang MY, Cheng SY, Zhang YJ, Wang XM, Lu YY, Wu NP, Mei LL, Wang ZX. Related Articles, Lir

Molecular biological analysis of genotyping and phylogeny of severe acute respiratory syndrome associated coronavirus.

Chin Med J (Engl). 2004 Jan;117(1):42-8.
PMID: 14733771 [PubMed - in process]

☐ 17: Mehta P, Casjens S, Krishnaswamy S. Related Articles, Lir

Analysis of the lambdoid prophage element e14 in the E. coli K-12 genome
BMC Microbiol. 2004 Jan 20;4(1):4.
PMID: 14733619 [PubMed - as supplied by publisher]

☐ 18: Wollerton MC, Gooding C, Wagner EJ, Garcia-Blanco MA, Smith CW. Related Articles, Lir

Autoregulation of polypyrimidine tract binding protein by alternative splicing leading to nonsense-mediated decay.
Mol Cell. 2004 Jan 16;13(1):91-100.
PMID: 14731397 [PubMed - in process]

☐ 19: Bunai K, Ariga M, Inoue T, Nozaki M, Ogane S, Kakeshita H, Nemoto T, Nakanishi H, Yamane K. Related Articles, Lir

Profiling and comprehensive expression analysis of ABC transporter solute binding proteins of Bacillus subtilis membrane based on a proteomic approach.
Electrophoresis. 2004 Jan;25(1):141-55.
PMID: 14730579 [PubMed - in process]

☐ 20: Xiao Z, Conrads TP, Lucas DA, Janini GM, Schaefer CF, Buetow KH, Issaq HJ, Veenstra TD. Related Articles, Lir

Direct ampholyte-free liquid-phase isoelectric peptide focusing: application to the human serum proteome.
Electrophoresis. 2004 Jan;25(1):128-33.
PMID: 14730577 [PubMed - in process]

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☐ **21:** Chu Z, Ouyang Y, Zhang J, Yang H, Wang S. Related Articles, Lir

Genome-wide analysis of defense-responsive genes in bacterial blight resistance of rice mediated by the recessive R gene xa13.
Mol Genet Genomics. 2004 Jan 17 [Epub ahead of print]
PMID: 14730444 [PubMed - as supplied by publisher]

☐ **22:** Hernanz-Falcon P, Rodriguez-Frade JM, Serrano A, Juan D, del Sol A, Soriano SF, Roncal F, Gomez L, Valencia A, Martinez-A C, Mellado M. Related Articles, Lir

Identification of amino acid residues crucial for chemokine receptor dimerization.
Nat Immunol. 2004 Feb;5(2):216-23. Epub 2004 Jan 11.
PMID: 14716309 [PubMed - in process]

☐ **23:** Margalit H, Altuvia Y. Related Articles, Lir

Insights from MHC-bound peptides.
Novartis Found Symp. 2003;254:77-90; discussion 91-101, 216-22, 250-2. Review.
PMID: 14712933 [PubMed - indexed for MEDLINE]

☐ **24:** Rammensee HG. Related Articles, Lir

Immunoinformatics: bioinformatic strategies for better understanding of immune function. Introduction.
Novartis Found Symp. 2003;254:1-2. No abstract available.
PMID: 14712928 [PubMed - indexed for MEDLINE]

☐ **25:** Brown SE, Cao AT, Hines ER, Akhurst RJ, East PD. Related Articles, Lir

A novel secreted protein toxin from the insect-pathogenic bacterium Xenorhabdus nematophila.
J Biol Chem. 2004 Jan 5 [Epub ahead of print]
PMID: 14707137 [PubMed - as supplied by publisher]

☐ **26:** Regeard C, Maillard J, Holliger C. Related Articles, Lir

Development of degenerate and specific PCR primers for the detection and isolation of known and putative chloroethene reductive dehalogenase genes
J Microbiol Methods. 2004 Jan;56(1):107-18.
PMID: 14706755 [PubMed - in process]

☐ **27:** Lei B, Liu M, Chesney GL, Musser JM. Related Articles, Lir

Identification of new candidate vaccine antigens made by Streptococcus pyogenes: purification and characterization of 16 putative extracellular lipoproteins.

J Infect Dis. 2004 Jan 1;189(1):79-89. Epub 2003 Dec 22.
PMID: 14702157 [PubMed - in process]

☐ 28: Minocha R, Studley K, Saier MH Jr. Related Articles, Lir

The urea transporter (UT) family: bioinformatic analyses leading to structural, functional, and evolutionary predictions.
Receptors Channels. 2003;9(6):345-52.
PMID: 14698962 [PubMed - in process]

☐ 29: Retta SF, Avolio M, Francalanci F, Procida S, Balzac F, Degani S, Tarone G, Silengo L. Related Articles, Lir

Identification of Krit1B: a novel alternative splicing isoform of cerebral cavernous malformation gene-1.
Gene. 2004 Jan 21;325:63-78.
PMID: 14697511 [PubMed - in process]

☐ 30: Selim AA, Abdelmagid SM, Kanaan RA, Smock SL, Owen TA, Popoff SN, Safadi FF. Related Articles, Lir

Anti-osteoactivin antibody inhibits osteoblast differentiation and function i vitro.
Crit Rev Eukaryot Gene Expr. 2003;13(2-4):265-75.
PMID: 14696973 [PubMed - in process]

☐ 31: Sinz A. Related Articles, Lir

Chemical cross-linking and mass spectrometry for mapping three-dimensional structures of proteins and protein complexes.
J Mass Spectrom. 2003 Dec;38(12):1225-37.
PMID: 14696200 [PubMed - in process]

☐ 32: Kleiger G, Panina EM, Mallick P, Eisenberg D. Related Articles, Lir

PFIT and PFRIT: bioinformatic algorithms for detecting glycosidase function from structure and sequence.
Protein Sci. 2004 Jan;13(1):221-9.
PMID: 14691237 [PubMed - in process]

☐ 33: de Bono B, Trowsdale J. Related Articles, Lir

Exploring the immunogenome with bioinformatics.
Semin Immunol. 2003 Aug;15(4):233-8.
PMID: 14690048 [PubMed - in process]

☐ 34: Vlahou A, Schorge JO, Gregory BW, Coleman RL. Related Articles, Lir

Diagnosis of Ovarian Cancer Using Decision Tree Classification of Mass Spectral Data.
J Biomed Biotechnol. 2003;2003(5):308-314.
PMID: 14688417 [PubMed - as supplied by publisher]

☐ 35: Ferrini JB, Jbilo O, Peleraux A, Combes T, Vidal H, Galiegue S, Casellas P. Related Articles, Lir

Transcriptomic classification of antitumor agents: application to the analys of the antitumoral effect of SR31747A.
Gene Expr. 2003;11(3-4):125-39.
PMID: 14686786 [PubMed - indexed for MEDLINE]

☐ 36: Lisitsa A, Archakov A, Lewi P, Janssen P. Related Articles, Lir

Bioinformatic insight into the unity and diversity of cytochromes P450.

Methods Find Exp Clin Pharmacol. 2003 Nov;25(9):733-45.
PMID: 14685302 [PubMed - in process]

☐ 37: Barre A, de Daruvar A, Blanchard A. Related Articles, Lir

MolliGen, a database dedicated to the comparative genomics of Mollicutes
Nucleic Acids Res. 2004 Jan 1;32 Database issue:D307-10.
PMID: 14681420 [PubMed - indexed for MEDLINE]

☐ 38: Lauterbach SB, Lanzillotti R, Coetzer TL. Related Articles, Lir

Construction and use of Plasmodium falciparum phage display libraries to identify host parasite interactions.
Malar J. 2003 Dec 17;2(1):47.
PMID: 14678570 [PubMed - as supplied by publisher]

☐ 39: Dudda-Subramanya R, Lucchese G, Kanduc D, Sinha AA. Related Articles, Lir

Clinical applications of DNA microarray analysis.
J Exp Ther Oncol. 2003 Nov-Dec;3(6):297-304.
PMID: 14678518 [PubMed - in process]

☐ 40: McBride MW, Charchar FJ, Graham D, Miller WH, Strahorn P, Carr FJ, Dominiczak AF. Related Articles, Lir

Functional genomics in rodent models of hypertension.
J Physiol. 2004 Jan 1;554(Pt 1):56-63.
PMID: 14678491 [PubMed - in process]

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41: Valdes J, Veloso F, Jedlicki E, Holmes D. Related Articles, Lir

Metabolic reconstruction of sulfur assimilation in the extremophile Acidithiobacillus ferrooxidans based on genome analysis.
BMC Genomics. 2003 Dec 15;4(1):51.
PMID: 14675496 [PubMed - as supplied by publisher]

42: Cherny I, Gazit E. Related Articles, Lir

The YefM antitoxin defines a family of natively unfolded proteins: Implications as a novel antibacterial target.
J Biol Chem. 2003 Dec 14 [Epub ahead of print]
PMID: 14672926 [PubMed - as supplied by publisher]

43: Donahue CP, Kosik KS. Related Articles, Lir

Distribution pattern of Notch3 mutations suggests a gain-of-function mechanism for CADASIL.
Genomics. 2004 Jan;83(1):59-65.
PMID: 14667809 [PubMed - in process]

44: Kurowski MA, Bhagwat AS, Papaj G, Bujnicki JM. Related Articles, Lir

Phylogenomic identification of five new human homologs of the DNA repa enzyme AlkB.
BMC Genomics. 2003 Dec 10;4(1):48.
PMID: 14667252 [PubMed - as supplied by publisher]

45: Wall T, Roos S, Jacobsson K, Rosander A, Jonsson H. Related Articles, Lir

Phage display reveals 52 novel extracellular and transmembrane proteins from Lactobacillus reuteri DSM 20016(T).
Microbiology. 2003 Dec;149(Pt 12):3493-505.
PMID: 14663082 [PubMed - in process]

46: Kim CA, Bowie JU. Related Articles, Lir

SAM domains: uniform structure, diversity of function.
Trends Biochem Sci. 2003 Dec;28(12):625-8.
PMID: 14659692 [PubMed - indexed for MEDLINE]

47: Strong M, Graeber TG, Beeby M, Pellegrini M, Thompson MJ, Yeates TO, Eisenberg D. Related Articles, Lir

Visualization and interpretation of protein networks in Mycobacterium tuberculosis based on hierarchical clustering of genome-wide functional linkage maps.
Nucleic Acids Res. 2003 Dec 15;31(24):7099-109.

PMID: 14654685 [PubMed - indexed for MEDLINE]

☐ 48: Bera TK, Hahn Y, Lee B, Pastan IH. Related Articles, Lir

TEPP, a new gene specifically expressed in testis, prostate, and placenta an well conserved in chordates.
Biochem Biophys Res Commun. 2003 Dec 26;312(4):1209-15.
PMID: 14652002 [PubMed - in process]

☐ 49: Buttner D, Noel L, Thieme F, Bonas U. Related Articles, Lir

Genomic approaches in Xanthomonas campestris pv. vesicatoria allow fishing for virulence genes.
J Biotechnol. 2003 Dec 19;106(2-3):203-14.
PMID: 14651862 [PubMed - in process]

☐ 50: Ramussen JP, Taylor AH, Ma LJ, Purcell S, Kempken F, Catcheside DE. Related Articles, Lir

Guest, a transposable element belonging to the Tc1/mariner superfamily is an ancient invader of Neurospora genomes.
Fungal Genet Biol. 2004 Jan;41(1):52-61.
PMID: 14643259 [PubMed - in process]

☐ 51: Rowland JJ. Related Articles, Lir

Model selection methodology in supervised learning with evolutionary computation.
Biosystems. 2003 Nov;72(1-2):187-96.
PMID: 14642667 [PubMed - in process]

☐ 52: Thongboonkerd V, Klein JB. Related Articles, Lir

Practical bioinformatics for proteomics.
Contrib Nephrol. 2004;141:79-92. Review.
PMID: 14650226 [PubMed - indexed for MEDLINE]

☐ 53: Abergel C, Coutard B, Byrne D, Chenivesse S, Claude JB, Deregnaucourt C, Fricaux T, Gianesini-Boutreux C, Jeudy S, Lebrun R, Maza C, Notredame C, Poirot O, Suhre K, Varagnol M, Claverie JM. Lir

Structural genomics of highly conserved microbial genes of unknown function in search of new antibacterial targets.
J Struct Funct Genomics. 2003;4(2-3):141-57.
PMID: 14649299 [PubMed - in process]

☐ 54: Jensen MA, Li FS, van 't Wout AB, Nickle DC, Shriner D, He HX, McLaughlin S, Shankarappa R, Margolick JB, Mullins JI. Related Articles, Lir

Improved coreceptor usage prediction and genotypic monitoring of R5-to-X transition by motif analysis of human immunodeficiency virus type 1 env V loop sequences.
J Virol. 2003 Dec;77(24):13376-88.
PMID: 14645592 [PubMed - indexed for MEDLINE]

☐ 55: Flower DR. Related Articles, Lir

Towards in silico prediction of immunogenic epitopes.
Trends Immunol. 2003 Dec;24(12):667-74. Review.
PMID: 14644141 [PubMed - indexed for MEDLINE]

☐ 56: Cai X, Lytton J. Related Articles, Lir

Molecular Cloning of a Sixth Member of the K+-dependent Na+/Ca2+

Exchanger Gene Family, NCKX6.
J Biol Chem. 2004 Feb 13;279(7):5867-76. Epub 2003 Nov 18.
PMID: 14625281 [PubMed - in process]

☐ 57: Cubero E, Abrescia NG, Subirana JA, Luque FJ, Orozco M. Related Articles, Lir

Theoretical study of a new DNA structure: the antiparallel Hoogsteen duplex.
J Am Chem Soc. 2003 Nov 26;125(47):14603-12.
PMID: 14624611 [PubMed - indexed for MEDLINE]

☐ 58: Davidson A, Siddell S. Related Articles, Lir

Potential for antiviral treatment of severe acute respiratory syndrome.
Curr Opin Infect Dis. 2003 Dec;16(6):565-71.
PMID: 14624107 [PubMed - in process]

☐ 59: Liebel U, Starkuviene V, Erfle H, Simpson JC, Poustka A, Wiemann S, Pepperkok R. Related Articles, Lir

A microscope-based screening platform for large-scale functional protein analysis in intact cells.
FEBS Lett. 2003 Nov 20;554(3):394-8.
PMID: 14623100 [PubMed - indexed for MEDLINE]

☐ 60: Jacobs MA, Alwood A, Thaipisuttikul I, Spencer D, Haugen E, Ernst S, Will O, Kaul R, Raymond C, Levy R, Chun-Rong L, Guenthner D, Bovee D, Olson MV, Manoil C. Related Articles, Lir

Comprehensive transposon mutant library of Pseudomonas aeruginosa.
Proc Natl Acad Sci U S A. 2003 Nov 25;100(24):14339-44. Epub 2003 Nov 14.
PMID: 14617778 [PubMed - indexed for MEDLINE]

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1: Gene. 2002 Sep 18;298(1):1-7.

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The human SLC8A3 gene and the tissue-specific Na+/Ca2+ exchanger 3 isoforms.

Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E.

Department of Biological Chemistry, University of Padova, Via G. Colombo 3, 35121 Padua, Italy. nadia.gabellini@unipd.it

We have identified the human gene for member 3 of Solute Carrier family 8 (SLC8A3) by bioinformatic analysis of human genomic sequences. The gene located on chromosome 14q24.2, and spans a region of about 150 kb. The fu length DNA complementary to RNA encoding the Na(+)/Ca(2+) exchanger isoform 3 (NCX3), amplified by reverse transcriptase-polymerase chain reaction (RT-PCR) from the human neuroblastoma SH-SY5Y RNA, includes seven exons and encodes a protein of about 100 kDa. RT-PCR analysis was performed in different tissues to determine the exon composition in the regio encoding the large intracellular loop of the protein. The region underwent modifications by alternative tissue-specific splicing. NCX3.2, including exor but not exon 5, was found in human brain and in the neuroblastoma cell line. human skeletal muscle two additional isoforms were identified: NCX3.3, including exons 4 and 5, and a truncated isoform (NCX3.4) produced by the skipping of both exons 3 and 4. The skipping causes a frame shift downstrea of the exon 2 sequence. The new coding sequence of 25 amino acids termina with a stop codon in exon 6. The NCX3.4 isoform (68 kDa) is truncated in th C-terminal portion of the domain first found in Drosophila Na(+)/Ca(2+) exchanger domain (Calxbeta) and lacks the C-terminal hydrophobic segment

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The gene promoter of human Na+/Ca2+ exchanger isoform 3 (SLC8A3) is controlled by cAMP and calcium.

Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E.

Department of Biological Chemistry, University of Padua, 35121 Padua, Ital
nadia.gabellini@unipd.it

PMID: 12502570 [PubMed - indexed for MEDLINE]

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1: J Neurochem. 2003 Jan;84(2):282-93.

Control of the Na+/Ca2+ exchanger 3 promoter by cyclic adenosine monophosphate and Ca2+ in differentiating neurons.

Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E.

Department of Biological Chemistry, University of Padova, Italy.
nadia.gabellini@unipd.it

The human gene for member 3 of solute carrier family 8 (SLC8A3), encodin the Na+/Ca2+ exchanger isoform 3 (NCX3), was identified on chromosome 14q24.2. The minimal promoter region was predicted 250 bp upstream of ex 1. This was confirmed by luciferase reporter assays of pGL3-promoter constructs in transfected SH-SY5Y cells. The promoter activity was monitor during the differentiation of this cell line elicited by the sequential treatment with retinoic acid and brain-derived neurotrophic factor (BDNF). The activit was induced by cyclic AMP (cAMP) via the CRE (cAMP response element) and was stimulated by retinoic acid. The increase of intracellular Ca2+ induc by the partial depolarization of the plasma membrane with KCl down-regulat both the basal and the cAMP-stimulated transcription. The down-regulation the latter may be mediated by the phosphorylation of the CRE-binding protei by a calmodulin-dependent kinase (CaMKII). The exposure of cells to BDNI after treatment with retinoic acid rapidly induced promoter activity during th initial five hours and phosphorylation of CRE-binding protein during the firs two hours. The promoter activity was further enhanced by cAMP, but becam insensitive to Ca2+. In BDNF-stimulated cells cAMP elevation caused the preferential phosphorylation of ATF1 instead of that of CRE-binding protein

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